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Lack of large genomic deletions in *BRIP1*, *PALB2*, and *FANCD2* genes in *BRCA1/2* negative familial breast cancer

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To the editor

Breast cancer (BC) is the most common malignancy in women worldwide. It is estimated that 5–10% of all BC cases may be caused by germline mutations in breast cancer susceptibility genes [19, 21]. *BRCA1* and *BRCA2* are the major known BC susceptibility genes accounting for ~16% of the familial BC cases [2]. Other BC susceptibility genes include *TP53* [16], *PTEN* [15], *ATM* [24], *LKB1/STK11* [8], *CHEK2* [28], *BRIP1/FANCI* [27], and *PALB2/FANCD2* [22]. However to date, the majority of familial BC cases can not be attributed to mutations in one of the known susceptibility genes.

The discovery of the breast cancer susceptibility gene *BRCA2* as the gene defective in the Fanconi anemia (FA)-D1 complementation group [11], the identification of *BRIP1* (BRCA1 Interacting Protein) [3, 12, 13] and *PALB2* (Partner And Localizer of BRCA2) [23, 32] as the genes responsible for the FA-J and FA-N complementation groups, respectively, established a clear link between breast cancer susceptibility and FA. Fanconi anemia (FA) is a recessively

inherited chromosomal instability syndrome with autosomal or X-linked mode of inheritance, and is characterized by an increased susceptibility to several forms of malignancies [1, 17]. The disease is caused by mutations in one of the 13 genes so far identified [18]. The FA gene products interact in a common pathway whereby most of the proteins (FANCA, -B, -C, -E, -F, -G, -L, and -M) form a multiprotein complex that is required for the monoubiquitination of FANCD2 and FANCI. However, this modification step is not influenced by FANCD1 (BRCA2), FANCI (BRIP1), or FANCD2 (PALB2), and hence these proteins seem to act downstream of this process. FANCD2 and FANCI are thought to form a protein complex (ID complex), which translocates to DNA damage sites where it co-localizes with the downstream FA proteins, BRCA2/FANCD1, BRIP1/FANCI, and PALB2/FANCD2 and other proteins that are involved in the recognition and repair of DNA damage, such as BRCA1, ATM, NBS, and RAD51 [31].

Several studies explored whether heterozygous female carriers for a mutation in one of the FA genes are at increased risk for breast cancer. To date, only mutations in the “downstream” FA genes have been found to significantly elevate the risk of developing breast cancer. Heterozygous mutations in *BRIP1/FANCI* and *PALB2/FANCD2* appear to increase the risk 2- and 2.3-fold, respectively [22, 27]. Risk assessment has been based on screening for truncating mutations in these genes in familial breast cancer (FBC) patients lacking mutations in *BRCA1/2*. Furthermore, *FANCD2* mutations, have been suggested to play a role in the development of breast cancer based on observations of *Fancd2* knockout mice, which demonstrated a high incidence of epithelial tumors, including mammary and ovarian tumors [10]. However, in humans a significant contribution of *FANCD2* mutations to FBC could not be established [14, 26].

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Interestingly, one of the eight FA-N patients described in literature carried a pathogenic nucleotide substitution on one allele and a large genomic deletion encompassing exon 1 through 10 of *PALB2/FANCN* on the other allele [32]. The latter aberration is not detectable by standard sequencing methods applied for *PALB2/FANCN* mutation screening in most studies published to date [4, 5, 7, 9, 22, 29]. Although, large deletion analysis of *PALB2* has been assayed in BC patients from French-Canadian and northern-Finnish ancestry, these cohorts were relatively small [6, 20]. In addition, such genetic aberrations may be very rare in the analyzed populations. Analysis of large deletions in *BRIP1/FANCF* and *FANCD2* has not been previously described in literature.

Since large deletion mutations have not been extensively studied, we hypothesized that such aberrations in the downstream FA genes (*FANCF* and *FANCN*) and *FANCD2* may contribute to the risk of breast cancer in familial cases. In the current study, we analyzed a total of 716 unrelated Dutch *BRCA1/2* negative familial breast cancer patients (inclusion criteria have described elsewhere [30] for large genomic deletions in *BRIP1/FANCF*, *PALB2/FANCN*, and *FANCD2* using Multiplex Ligation-dependent Probe Amplification (MLPA; [25]). We failed to detect deletions in any of these genes. The MLPA kits used for the analysis contained probes targeted against all the exons of *BRIP1/FANCF* and *PALB2/FANCN*. Due to the presence of *FANCD2* pseudogenes, only a number of *FANCD2* exons could be analyzed (exons: 1, 2, 4, 9, 12, 17, 19, 23, 28, 32, 35, 41, 43) by MLPA. Large deletions encompassing multiple exons will be detected by the used MLPA kits, but subtle deletions/amplifications in the intronic regions and of *FANCD2* exons of which no probes were present in the MLPA kit could have been missed. In addition, genetic rearrangements such as inversions are not detectable by MLPA.

Our results suggest that large genomic deletions in *BRIP1/FANCF*, *PALB2/FANCN*, and *FANCD2* do not contribute significantly to the FBC risk in the Dutch population. In addition, no large deletions in *PALB2/FANCN* were observed in two previous studies where 43 FBC patients of French-Canadian ancestry [6] and 61 index patients of breast and/or ovarian cancer families from Northern Finland [20] were analyzed. The only known FA patient with a large deletion in *PALB2/FANCN* is of Argentinean nationality, this mutation might be derived from a founder of this particular population [32]. It may therefore be of interest to test FBC patients from the same population for the presence of this large deletion. Altogether, large genomic rearrangements in the studied genes may be very rare and the analysis of additional large cohorts of FBC patients from different populations may be necessary to determine the contribution of such aberrations to breast cancer risk.

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